REMARKS

Claims 14-21, 23-26, 28-36 and 38 are currently pending. Claims 14, 23, 28-30, and 32 have been amended. The amendments to claims 14, 23, 28-30, and 32 do not constitute new matter.

The Examiner has rejected claims 14-21, 23-26, 28-36, and 38 under 35 U.S.C. § 112, first paragraph, as lacking enablement. The Examiner has rejected claims 14-21, 23-26, 28-36, and 38 under 35 U.S.C. § 112, first paragraph, as lacking support in the written description.

For the reasons detailed below, the rejections should be withdrawn and the claims allowed to issue. Entry of the foregoing amendments is respectfully requested.

The Claims Are Enabled

The Examiner has rejected claims 14-21, 23-26, 28-36, and 38 under 35 U.S.C. § 112, first paragraph, as lacking enablement. The Examiner states that because bone marrow contains multiple cell types it "is unclear how unrelated and terminally differentiated cell types such as red cells or stromal cells can be cultured into mature [dendritic Langerhans cells (DLCs)].... it is most likely that only the monocytes found in the mouse bone marrow actually cultured into mature DLCs." The Examiner also contends that the specification does not provide sufficient evidence to show that the claimed methods actually result in mature DLCs.

Applicants assert that the Examiner is utilizing an improper standard, and that the specification sufficiently describes the claimed methods such that a person of ordinary skill in the art would be able to practice the invention. The Examiner is improperly requiring that the claimed method function perfectly, that is, that every cell present in the preparation should give rise to a DLC. Essentially, the Examiner contends that the invention is inoperative because there

are cells present which do not become DLCs, and therefore the invention is not enabled because it lacks utility. See MPEP § 2164.07 (if an invention is "shown to be nonuseful or inoperative, then it necessarily fails to meet the how-to-use aspect of the enablement requirement."). However, Applicants note that it is not required for a claimed invention to function perfectly, and operation of the invention need not be shown "beyond a reasonable doubt." See *Id.*; see also MPEP § 2164.08(a) (the presence of inoperable subject matter does not render an invention non-enabled). In the present case, it is not required that the specification provide evidence that every cell in the bone marrow preparation will give rise to an DLC. A person of ordinary skill in the art would understand that bone marrow cells contain cells which can develop into mature DLCs, and that not every cell found in bone marrow would be expected to develop into a mature DLC. Although not every cell from the bone marrow will develop into a DLC, this is irrelevant with regard to the enablement requirement; the invention, as claimed, is directed only to the production of a preparation comprising DLC, not a pure preparation consisting only of DLC. MPEP § 2164.08 ("the focus of the examination inquiry is whether everything within the scope of the claim is enabled.... the Examiner should determine what each claim recites and what the subject matter is when the claim is analyzed as a whole, not when its parts are analyzed individually.") (emphasis in original). Based upon the present disclosure, a person of ordinary skill in the art would be capable of producing DLCs from bone marrow, even if not all bone marrow cells will become DLCs. Accordingly, Applicants submit that the specification provides sufficient information to adequately enable the present invention, because it discloses that DLCs may be produced from bone marrow cells.

Similarly, the Examiner is utilizing an improper standard regarding the expression of cell surface markers on the DLCs resulting from the claimed method. Applicants submit that the

specification provides sufficient data to show the production of mature DLCs. Applicants note that the distinction between mature and immature DLCs does not lie in the absolute presence or absence of expression of particular cell surface markers, but instead depends upon the ability of the DLCs to stimulate T-cells. See Satthaporn *et al.*, J. R. Coll. Surg. Edinb., 2001, 46:9-19, 5-6 ("Satthaporn") (already of record). Satthaporn discloses that the ability to stimulate T-cells is largely dependent upon the expression of MHC class II molecules and costimulatory molecules on the surface of the cell. *Id.* The present specification discloses that 98.4% of the cells express HLA-DR, which is a type of MHC class II molecule. See the specification at page 8. Furthermore, 57.3% of the cells express the costimulatory molecule CD86, and approximately 20% express the costimulatory molecule CD80. *Id.* A person of ordinary skill in the art would understand that this data shows that the cells produced by the present method are capable of presenting antigens to T-cells and providing costimulation, and are therefore mature. In addition, the presence of CD40 on the cells, as well as the virtual absence of CD3 or CD19, indicates that these cells are dendritic cells, not B-cells or T-cells. See Brand *et al.*, Arch. Dermatol. Res., 1999, 291-65-72, 67 ("Brand"). Applicants further note that, while Brand teaches the presence of CD1a positively identifies a cell as being a DLC, Brand does not teach that the absence of CD1a confirm that a cell is *not* a DLC. Accordingly, because the invention need not work perfectly, as noted above, the showing that approximately 20% of the cells express CD1a, CD1b, CD80, and CD83 is sufficient to show that at least a portion of these cells are DLCs. Furthermore, the specification provides enough information for a person of ordinary skill in the art to produce DLCs via the claimed method, and by identifying the relevant markers, provides sufficient information for a person of ordinary skill in the art to test the cells to determine whether or not they are DLCs. Because methods of testing the cells are disclosed in the

specification, for example, at pages 6-7, and because the methods are well known in the art, such testing will be merely routine.

Based upon the foregoing, Applicants assert that the present invention is enabled, and respectfully request that the rejections be withdrawn.

The Claims Are Supported By The Specification

The Examiner has rejected claims 14-21, 23-26, 28-36, and 38 under 35 U.S.C. § 112, first paragraph, as lacking support in the written description. The Examiner's rejections are discussed in more detail below.

The Examiner has rejected claims 14, 23, 28-30, and 32, stating that the specification does not provide adequate support for the "monitoring" and "confirming" steps. The Examiner states that the specification "does not disclose the broad method of the instant claims" and that the specification "does not disclose a specific 'monitoring' of the appearance of dendritic morphology nor the specific 'confirming' the presence of the dendritic processes."

Applicants note that claims 14, 23, 28-30, and 32 have been amended to more particularly describe the claimed invention. The claims now recite monitoring for "dendritic processes and markers associated with dendritic Langerhans cells" and no longer recite "confirming the presence of dendritic processes." These amendments are supported by the specification at pages 7-8. The specification explicitly states that "[i]mmunophenotyping of *in vitro* generated human dendritic Langerhans type cells was performed by flow cytometry." However, Applicants note that explicit support in the specification is not necessary, and that implicit or inherent support is sufficient. MPEP § 2163 (claims may be supported "through express, implicit, or inherent disclosure."). The present specification provides several instances

where dendritic processes are monitored as a method of identifying the presence of dendritic Langerhans cells.

> When human monocytes were cultured in RPMI-1640 without FCS in the presence of rhGM-CSF and rhIL-4, there was hardly any transformation to immature DC with typical dendritic processes (not shown). However, when human peripheral blood monocytes were cultured in RPMI-1640 containing 2% FCS in the presence of 500 U/ml of rhGM-CSF and 500 U/ml of rhIL-4, transformation to immature dendritic cells (DC) with typical dendritic processes was noticed, as expected (Fig.1C). In parallel cultures of human monocytes in FCS free medium when autologous platelets were added instead of rhGM-CSF and rhIL-4 proliferating cells with dendritic processes started appearing within five to six days. Fig.1B shows growing colonies that developed when autologous platelets were added to serum-free human monocyte cultures. Morphologically these cells were similar to that generated in the presence of rhGM-CSF and rhIL-4. Of course, the presence of 2% FCS in human monocyte cultures containing autologous platelets accelerated the process of colony formation of cells with typical dendritic morphology. Typical dendritic processes of these cells grown in RPMI-1640 containing 2% FCS and autologous platelets are shown in Fig.1D. Platelets collected from allogeneic donors were as effective as autologous platelets in inducing growth of cells with dendritic processes from human monocytes.

See the specification at pages 7-8 (emphasis added). This disclosure implicitly supports the step of monitoring the cell cultures for the appearance of dendritic morphology, since the appearance of dendritic processes was utilized as a method of identifying the growth of dendritic Langerhans cells.

The Examiner has rejected claims 23, 29, 30, and 32, stating that the specification discloses only incubation at about 30°C to about 40°C. For the purposes of furthering prosecution, and without making any admissions, Applicants have amended claims 23, 29, 30, and 32 to recite that the cells are cultured or incubated "at about 30°C to about 40°C."

The Examiner has rejected claim 30, stating that the specification only discloses a method of producing mouse DLCs employing rat platelets, but not the specific combination of producing mouse DLCs with rat bone marrow and mouse platelets. For the purposes of furthering

prosecution, and without making any admissions, Applicants have amended claim 30 to specifically recite rat platelets and mouse bone marrow.

The Examiner has rejected claim 32, stating that the cited support at page 8 provides only a single example. The Examiner also states that the cited support states "only approximately 20%" instead of the "approximately 20%" recited in the claims. With regard to the number of examples, Applicants submit that the amount of examples provided in the specification is not relevant with regard to satisfying the written description requirement. The standard for satisfying the written description requirement is whether the specification provides enough information to show that the Applicants had possession of the claimed invention at the time of filing; one example may be sufficient to satisfy this requirement if it provides sufficient information. See MPEP § 2163. One method of showing possession is by actual reduction to practice. *Id.* ("Possession may be shown in a variety of ways including description of an actual reduction to practice."). In the present case, the example at pages 7-9 and data shown in Figure show that the claimed method was actually performed, and the resulting DLCs were immunophenotyped via flow cytometry. See the specification at pages 7-9. Accordingly, this description of actual reduction to practice is sufficient to show possession of the claimed invention and satisfy the written description requirement. With regard to the specification stating "only approximately 20%," Applicants submit that the word "only" is being used in a conversational manner to express contrast between the expression of CD1b, CD80, and CD83, as opposed to the expression of HLA-DR, CD40, and CD86. The term only is not an essential limitation, and does not effect the breadth of the claim. Applicants further note that the use of relative terminology, such as "approximately," is an accepted practice, and that the term

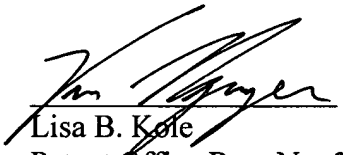
encompasses a flexible range of values. See MPEP § 2173.05(b). Accordingly, the addition of the term "only" would not provide any further clarification or limitation to the claim.

Based upon the foregoing, Applicants submit that the claims are fully supported by the specification, and respectfully request withdrawal of the rejections.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. The Applicant believes that the inventions described and defined by claims 14-21, 23-26, 28-36 and 38 are patentable over the rejections of the Examiner. Withdrawal of all rejections and reconsideration of the amended claims is requested. An early allowance is earnestly sought.

Respectfully submitted,



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